REMARKS

A listing of the pending claims is provided for the Examiner's convenience. No claim amendments are made herein. Claims 13-17 and 21-23 are presently pending. The following addresses the substance of the Office Action.

Obviousness

Claims 13, 14, 17, 21 and 22 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mishra et al. (1993 *Cancer Research* **53**:557-563). Mishra et al. teaches that O-phospho-L-tyrosine (P-Tyr) inhibits cellular growth of human breast and renal carcinoma cells and that P-Tyr also sensitizes ACHN cells to killing by chemotherapeutic agents doxorubicin and etoposide. Thus, the Examiner concluded that it would have been obvious to administer P-Tyr to a patient, and that administration of P-Tyr to patients with renal and/or breast carcinoma would inherently result in the selective protection of non-transformed.

The Applicant notes that Mishra et al. teaches the use of P-Tyr as an anticancer agent against isolated, renal carcinoma cell lines; see, page 557, abstract and page 562, last paragraph. In contrast, the instant application does not relate to an anticancer agent but rather to a protective substance, which selectively protects healthy, non-transformed cells from cell damaging factors. Although one of skill in the art would have understood that P-Tyr may work as an anticancer agent against transformed cells on the one hand, there was no expectation of success that it would also have a protective effect with non-transformed cells. Mishra et al. is completely silent on the fact that P-Tyr can be used as substance that selectively protects healthy non-transformed cells from cell-damaging factors. The Examiner concluded that administration of P-Tyr to patients with renal and/or breast carcinoma would inherently result in the selective protection of non-transformed. However, while the skilled artisan would have been motivated to target transformed, carcinoma cells with P-Tyr to kill the cells, there was no reason to specifically expose both non-transformed and transformed cells to P-Tyr before, during or after exposure to cell-damaging factors.

The inventors of the instant application have discovered a protective effect of P-Tyr on healthy skin fibroblasts (HSF6). In contrast, no protective effect (i.e., clonogenic survival) was observed in the case of transformed, non-healthy HH4dd fibroblasts. The inventors were able to demonstrate for the very first time, that the healthy cells are selectively protected by P-Tyr against radioactive radiation, whereas the transformed non-healthy cells are not; see Example 4, Fig. 2B. Furthermore, the inventors also demonstrated that healthy skin fibroblasts (HSF6) and healthy lung fibroblasts (CCD32) selectively survive ionizing radiation significantly better than transformed cells (HTB-35 HTB-43); See, Example 6, Fig. 4A, 4B. A corresponding selective protection has been demonstrated by the inventors for healthy skin fibroblasts (HSF6) in comparison to transformed fibroblasts (HH4dd) against non-ionizing radiation (UVB); See, Example 7, Fig. 5A, 5B. Finally, selective protection of non-transformed cells was demonstrated by the inventors of the instant application for the very first time in view of a treatment with the cytostatic agent cisplatin. Healthy fibroblasts (HSF1) were significantly better protected than transformed fibroblasts (HH4dd); See, Example 8, Fig. 6A, 6B.

The Applicant notes that Mishra et al. exclusively analyzed isolated tumor cell lines, namely the human renal carcinoma cell lines ACHN, Cakill, A704 and A498 and the human breast carcinoma cell line MDA-MB-468. Thus, the authors did not perform any experiments using healthy, non-transformed cells. Therefore, the only statement given by the authors is that, allegedly, the cell growth of these transformed tumor cells is inhibited by P-Tyr; see, Mishra et al. at page 560, left column, 1st paragraph. Additionally, every quotation made by the Examiner in the Office Action specifically refers to isolated tumor or carcinoma cells. In other words, Mishra et al. are completely silent on any effect of P-Tyr on healthy, non-transformed cells. In fact, the authors had no idea whether P-Tyr might have any effect on healthy, non-transformed cells, and if so, what kind of effect this might be. Neither Mishra et al. nor any other research group has treated a subject or a biological material comprising healthy, non-transformed and transformed cells by administering P-Tyr.

Moreover, the unbiased reader of Mishra et al. would assume that the alleged growth inhibitory effect on tumor cells as described by Mishra would also be observed with healthy, non-transformed cells. The authors assume that the growth arrest observed for the transformed cancer cells was due to a P-Tyr-mediated modulation of cellular PTPases; see Mishra et al. at page 560, right column, last paragraph and page 561, left column, 1st paragraph. However, PTPases are enzymes that are involved in the cellular signal transduction not only in cancer cells, but also in healthy, non-transformed cells; see Misra et al. at page 557, left column, "Introduction". Therefore, P-Tyr would have an influence on the modulation of cellular PTPases in tumor cells and in healthy cells. Accordingly, there was no reason for the skilled artisan to believe that there could be a selectivity of the action of P-Tyr, as discovered by the inventors. Mishra et al. neither provides any information on the effect of P-Tyr on healthy cells, nor on any selective activity thereof with regards to healthy cells in comparison to non-healthy, transformed cells.

In addition, the findings of Mishra et al. are generally disputed. This is based on the fact that the inventors of the instant application were not even able to demonstrate a growth inhibitory effect of P-Tyr on carcinoma cells as suggested by the authors. Referring to Example 4 at paragraphs [0071] and [0072] of the instant application, normal skin fibroblasts (HSF6) were incubated for 16 hours with P-Tyr at a concentration range of from 0 to 2000 μM. The clonogenic survival was then determined without any cell-damaging treatment. The result of such an experiment is shown in Fig. 2A. As Fig. 2A shows, pretreating with P-Tyr alone at concentrations of up to 2000 μM did not have any effect on the clonogenic survival of the HSF6 cells. Comparable results were obtained for the transformed fibroblast cell line HH4dd. Unexpectedly, in view of the results of Mishra et al., no effect was seen on clonogenic survival.

In view of the foregoing, Mishra et al. neither anticipates nor renders obvious the subject matter of the pending claims. As such, the Applicant respectfully requests that the rejection be withdrawn.

Claims 13-17 and 21-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Blomqvist et al. (1992 *British J Cancer* **66**:1171-1176) in view of Mishra et al. (*supra*). Blomqvist et al. teach that a combination of chemotherapy and radiotherapy give better local control of stage II breast cancer compared to either treatment alone. However, neither Blomqvist et al. nor Mishra et al. had any appreciation that P-Tyr could be used as substance that selectively protects healthy non-transformed cells from cell-damaging factors. Thus, as discussed above, while the skilled artisan would have been motivated by the cited references, either alone or in combination, to target transformed carcinoma cells with P-Tyr to kill the cells, there was no reason for the skilled artisan to specifically expose both non-transformed and transformed cells to P-Tyr before, during or after exposure to cell-damaging factors, so that the non-transformed biological cells would be selectively protected from cell damage as compared to transformed cells.

Accordingly, the present claimed methods are not *prima facie* obvious and the Applicant respectfully requests that the rejection be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: March 2, 2010

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